REMARKS

I. Preliminary Comments

Applicants note with gratitude that the Examiner has withdrawn or held in abeyance certain of the previous rejections. These include:

(5) In addition, the provisional obviousness-type double patenting rejection over copending application Serial No. 09/203,078 was held in abeyance.

(6) The obviousness-type double patenting rejection of Claims 70-226 over claims 12 and 31 of U.S. Patent 6,726,907 has been withdrawn in light of the filing of the terminal disclaimer.

(7) The written description rejection of claims 70-226 under 35 U.S.C. §112, first paragraph, relating to "a therapeutic adenovirus" has been withdrawn. In withdrawing the rejection the Examiner commented that "it is clear that Applicant's invention is not a method of gene therapy but a method of making adenovirus." Applicants' invention is what is defined by their claims which recite "methods of treating patients" and Applicants traverse any more limiting characterization.

(9) The Examiner withdrew the rejections of claims 70-71, 75-77, 83 and 85-100 under 35 U.S.C. §102(e) as being anticipated by Zhang et al., '010 as further evidenced by Huyghe, et al., Human Gene Therapy, 6:1403-1416 (1995). Note, that the Examiner did not withdraw this rejection against claim 73 noted below.

(10) The obviousness-type double patenting rejection of claims 70-226 over claims 1-89 of U.S. Patent 6,194,191 has been withdrawn in light of the filing of the terminal disclaimer.

II. The Outstanding Rejections

As discussed above, the Examiner withdrew a number of the previous rejections. In addition, the Examiner maintained, and in some cases elaborated upon the following rejections:

Maintained Rejections

(8) The lack of enablement rejection of claims 70-226 under 35 U.S.C. §112, first paragraph is maintained. In particular, the Examiner finds that the application does not provide enablement for treating disease by means other than:

> [g]rowing the cells at a low to medium perfusion rate of 1-2 g/L glucose, followed by detergent lysis with 1% Tween 20, a single anion exchange chromatography step in a Toyopearl Super Q 650 FPLC anion exchange column, and concentration/diafiltration and nuclease treatment.

The Examiner then responds to the arguments made in the Response filed October 25, 2005 with a list of reasons extending from pages 8-15 of the current Office Action. In particular the Examiner argues that:

> Applicant's claims are not limited to p53 and cervical cancer, but encompass all gene therapy, by any method of administration, with any transgene and operably linked expression regulatory elements.

(9) While the Examiner withdrew the rejections of claims 70-71, 75-77, 83 and 85-100, as noted above, the rejection of claim 73 under 35 U.S.C. §102(e) as being anticipated by Zhang et al., '010 as further evidenced by Huyghe, et al., Human Gene Therapy, 6:1403-1416 (1995) was maintained "because [it] does not require any BSA levels."

(11) The Examiner maintained the rejection of claims 70, 71 and 78-82 and 84 under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al. as further evidenced by Huyghe et al. as applied to claim 70 above, and further in view of Perrin et al., (1995) Vaccine, 13(13): 1244-50. In addition, the Examiner newly rejected claims 72-77, 83 and 85-100 under those references as applied to claim 73 and further in view of Perrin et al.

(12) Claim 74 remains rejected under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al. as further evidenced by Huyghe et al. and Nadeau et al., (1996) Biotechnology and Bioengineering, 51:613-623, or Trepanier et al., (1981) J. Virological Methods, 3: 201-11.

(13) Claims 101, 103-104 and 106-131 remain rejected (and claims 102 and 105 are newly rejected) under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al. as further evidenced by Huyghe et al as applied to claims 70-71, 73, 75-77, 83 and 85-100 above, and further in view of Perrin et al., (1995) Vaccine, 13(13): 1244-50.

(14) Claims 132, 134-135 and 137-162 remain rejected (and claims 133 and 136 are newly rejected) under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al. as further evidenced by Huyghe et al. and Perrin et al.

(15) Claim 105 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. as further evidenced by Huyghe et al. and further in view of Perrin et al. as applied to claim 101 above, and further in view of Nadeau et al. or Trepanier et al. (15)

(16) Claims 163, 165-166, 168-170, 176 and 178-198 remain rejected (and claims 164, 167 and 171 are newly rejected) under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al. as further evidenced by Huyghe et al. and in view of Graham et al, (1991) Methods in Molecular Biology, Vol. 7, Ed. By Murray, published by Humana Press, In., Clifton, NJ., pp. 109-128. (16)

(17) Claims 171-175 and 177 remain rejected (and claims 163-170 and 178-193 are newly rejected) under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al. as further evidenced by Huyghe et al. and Graham et al. as applied to claim 163 above, and further in view of Perrin et al.

(18) Claim 167 remains rejected under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al. as further evidenced by Huyghe et al. and in view of Graham et al., or as further referenced by Perrin et al and further in view of Nadeau et al. or Trepanier et al.

(19) Claims 194, 196-197, 199-201, 207 and 209-226 remain rejected (and claims 195, 198 and 202 are newly rejected) under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al. and Huyghe et al. as further evidenced by Huyghe et al.

(20) Claims 194, 202-206 and 208 remain rejected (and claims 195-201, 207 and 209-226 are newly rejected) under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al.

and Huyghe et al. as further evidenced by Huyghe as applied to claim 194 above, and further in view of Perrin et al.

(21) Claim 198 remains rejected under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al. and Huyghe et al. as further evidenced by Huyghe, and further in view of Nadeau et al.

New Rejections

Further, a number of new rejections were entered as set out below:

(22) Claims 149 and 150 are objected to as having improper dependencies which can be readily corrected by amendment.

(23) Claims 70-87, 91-118, 122-149, 153-180, 184-211 and 215-226 stand rejected under 35 U.S.C. §112 (first paragraph) for lack of enablement. Specifically, "[t]he presence of a therapeutic transgene is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure." This rejection seems to relate to previous rejection (7) under §112 (first paragraph) for lack of written description that was withdrawn after citation of the ONYX-015 adenovirus.

(24) Claims 70-87, 91-118, 122-149, 153-180, 184-211 and 215-226 stand rejected under 35 U.S.C. §112 (second paragraph) as lacking an essential element which is said to be a transgene. This also seems related to the previous rejection under §112 (first paragraph).

(25) Claims 78, 109, 140, 171 and 202 stand rejected under 35 U.S.C. 112 as failing to comply with the written description requirement with respect to the adenoviral composition being "essentially free of BSA." The Examiner did note that he found support for the previous claim language which recited "BSA levels below the detection limit of a western blot assay" so one option might be to re-amend those claims.

(26) Claims 70-72, 74-78, 83 and 85-100 stand newly rejected under 35 U.S.C. §102(e) as being anticipated by Zhang et al., '010 as further evidenced by Huyghe, et al., Human Gene Therapy, 6:1403-1416 (1995) under a new basis of rejection detailed at pages 16-19 of the Action. The Examiner acknowledges that "Zhang does not explicitly review how to manufacture the adenoviruses according to the steps recited..." but argues that "Huyghe teaches purification by cesium chloride and that "absent to believe otherwise, such produced adenovirus is essentially pure and contains BSA levels below the detection limit of a western blot assay, and is further essentially free of BSA."

III. Amendments

Claims 70, 72 and 73 have been amended to recite the limitation of claim 79 (now cancelled) that the media in which the host cells are grown is "serum-free."

Claims 163, 165 and 166 have been amended to recite the limitations of dependent claims 173 and 174 reciting that the host cells are grown "in a bioreactor or on a microcarrier."

Claims 194, 196 and 197 have been amended to recite the limitations of dependent claims 206 and 208 reciting that the nutrients are provided to the host cells "by perfusion or roller bottle process."

As will be discussed in greater detail below, the forgoing amendments place the claims in condition for allowance by removing **all** the outstanding art-based rejections with the exception of those relying on the disclosure of Perrin et al., (1995) Vaccine, 13(13): 1244-50! Applicants will address the remaining art rejections all based on the Perrin disclosure below along with the remaining rejection under 35 U.S.C. §112 (first paragraph) below.

III. Patentability Arguments

A. The Art-Based Rejections NOT Based on Perrin Should be Withdrawn.

The art-based rejections not based on Perrin et al. have all been obviated by the amendment of the independent claims to incorporate limitations of dependent claims only rejected by combinations of references including the Perrin reference.

Specifically, claims 70, 72 and 73 have been amended to recite the limitation of claim 79 (now cancelled) that the media in which the host cells are grown is "serum-free." Claim 79 was free of each of the following rejections:

> (9) Claim 73 under 35 U.S.C. §102(e) as being anticipated by Zhang et al., '010 as further evidenced by Huyghe, et al., Human Gene Therapy, 6:1403-1416 (1995).
>
> (12) Claim 74 under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al. as further evidenced by Huyghe et al. and Nadeau et al., (1996) Biotechnology and Bioengineering, 51:613-623, or Trepanier et al., (1981) J. Virological Methods, 3: 201-11.
>
> (26) Claims 70-72, 74-78, 83 and 85-100 rejected under 35 U.S.C. §102(e) as being anticipated by Zhang et al., '010 as further evidenced by Huyghe, et al., Human Gene Therapy, 6:1403-1416 (1995). .

Accordingly claims 70-78 and 80-100 now suffer an art-based rejection only under the combination of:

(11) Zhang et al. '010 as further evidenced by Huyghe et al. Human Gene Therapy, 6:1403-1416 (1995) and further in view of Perrin et al., (1995) Vaccine, 13(13): 1244-50.

Claims 163, 165 and 166 have been amended to recite the limitations of dependent claims 173 and 174 that the host cells are grown "in a bioreactor or on a microcarrier." Claims 173 and 174 were free of each of the following rejections:

> (16) Claims 163-171, 176 and 178-198 rejected under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al. as further evidenced by Huyghe et al. and in view of Graham et al, (1991) Methods in Molecular Biology, Vol. 7, Ed. By Murray, published by Humana Press, In., Clifton, NJ., pp. 109-128.
>
> (18) Claim 167 rejected under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al. as further evidenced by Huyghe et al. and in view of Graham et al., or as further referenced by

> Perrin et al and further in view of Nadeau et al. or Trepanier et al.

Accordingly claims 163-193 now suffer an art-based rejection only under the combination of Zhang et al. as further evidenced by Huyghe et al. and Graham et al. and further in view of Perrin et al.

Claims 194, 196 and 197 have been amended to recite the limitations of dependent claims 206 and 208 that the host cells are provided nutrition "by perfusion or a roller bottle process." Claims 206 and 208 were free of each of the following rejections:

> (16) Claims 163-171, 176 and 178-198 rejected under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al. as further evidenced by Huyghe et al. and in view of Graham et al, (1991) Methods in Molecular Biology, Vol. 7, Ed. By Murray, published by Humana Press, In., Clifton, NJ., pp. 109-128.
>
> (19) Claims 194-202, 207 and 209-226 rejected under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al. and Huyghe et al. as further evidenced by Huyghe et al.
>
> (21) Claim 198 rejected under 35 U.S.C. § 103(a) as being unpatentable over Zhang et al. and Huyghe et al. as further evidenced by Huyghe, and further in view of Nadeau et al.

Accordingly claims 194-226 now suffer an art-based rejection only under the combination (17) of Zhang et al. as further evidenced by Huyghe et al. and Graham et al. and further in view of Perrin et al.; or the combination (20) of Zhang et al. and Huyghe et al. as further evidenced by Huyghe, and further in view of Perrin et al.

B. The Art-Based Rejections Based on Perrin Should be Withdrawn.

1. Perrin Supplies the Missing Elements in all the Remaining Rejections.

With the amendment of independent claims 70, 72, 73, 101, 103, 104, 132, 134, 135, 163, 165, 166, 194, 196 and 197 to incorporate variously the limitations of dependent claims 79, 173, 174, 206 and 208 as described above, the art-based rejections not based on Perrin et al. have all been obviated and the only remaining art-based rejections of the claims are those

based on a combination of Perrin et al. together with Zhang et al. and Huyghe et al. or Perrin et al., together with Zhang et al., Huyghe et al. and Graham et al.

Specifically, these are:

> Claims 70-100, including claim 79 reciting the serum-free limitation that was incorporated into independent claims 70, 72 and 73 were all rejected as being obvious under 35 U.S.C. §103(a) over the combination of Zhang et al., Huyghe et al. and Perrin et al. (11)
>
> Claims 101-104 and 106-131 reciting the bioreactor and microcarrier limitations were all rejected as being obvious under 35 U.S.C. §103(a) over the combination of Zhang et al., Huyghe et al. and Perrin et al. (13) while claim 105 was rejected 35 U.S.C. §103(a) over the combination of Zhang et al., Huyghe et al. and Perrin et al. and further over Nadeau and Trepanier. (15)
>
> Claims 132-162 reciting the perfusion and roller bottle limitations were all rejected as being obvious under 35 U.S.C. §103(a) over the combination of Zhang et al., Huyghe et al. and Perrin et al. (14)
>
> Claims 163-175 and 177-193, including claims 173 and 174 reciting the bioreactor and microcarrier limitations that were incorporated into independent claims 163, 165 and 166 were all rejected as being obvious under 35 U.S.C. §103(a) over the combination of Zhang et al., Huyghe et al. and Graham et al. and Perrin et al. (16, 17)
>
> Claims 194-226, including claims 206 and 208 reciting the perfusion and roller bottle limitations that were incorporated into independent claims 194, 196 and 197 were all rejected as being obvious under 35 U.S.C. §103(a) over the combination of Zhang et al., Huyghe et al. and Graham et al. and Perrin et al. (20)

1. The Remaining Rejections All Rely Upon Perrin

The Examiner acknowledged that each of these combinations of references lacks an element that is only made up by the addition of Perrin to the combination. Thus, in the rejection of claims 70-100 over the combination of Zhang et al. and Huyghe et al. the Examiner acknowledged that "Zhang does not teach the aspects of serum free media, bioreactors, microcarriers, or perfusion methods" (Action page 20, lines 9-10) and Perrin is relied upon to teach the use of serum-free media.

Similarly, claims 101-131 stand rejected over the combination of Zhang et al., and Huyghe et al. optionally in combination with Nadeau and Trepanier when the Examiner acknowledged that "Zhang does not teach the aspects of bioreactors and/or microcariers..." (Action page 23, lines 20-21) this gap was filled by the teachings of Perrin et al. (Action page 24, lines 7-8).

Such was also the case with claims 132-162 where the combination of Zhang et al. and Huyghe et al. failed to "teach the aspects of perfusion, roller bottles, serum free media, bioreactors; or microreactors..." (Action page 28, lines 8-9) Instead, the Examiner relied upon Perrin et al. for disclosing the elements of elements of perfusion and roller bottles. (Action page 28, lines 17.)

This was also the case with claims 163-175 and 177-193 where the combination of Zhang et al., Huyghe et al. and Graham et al. all failed to "teach the aspects of bioreactors and/or microcarriers..." (Action page 36, lines 19-20) In this case Perrin was cited for the teaching of bioreactors with microcarriers. (Action page 37, line 8)

Finally, when claims 194-226 were rejected over the combination of Zhang et al., Huyghe et al. and Graham et al. those references failed to "teach, serum free media, bioreactors, microcarriers, perfusion techniques, or roller bottles." (Action page 43, lines 14-15) Instead, Perrin was relied upon as teaching the use of perfusion techniques and roller-bottles. (Action page 44, line 3).

2. Perrin Relates to a Rabies Virus System and is Irrelevant to an Adenovirus System

These art-based rejections that are based on Perrin et al. should each be withdrawn because Perrin is directed to a rabies virus system which is entirely irrelevant to Applicants' adenovirus claims. Not only is there no motivation to combine the teachings of any of the Zhang et al., Huyghe et al., Nadeau, Trepanier and Graham et al. references with the teachings of Perrin but Perrin in no way addresses the hurdle facing the combination of the Zhang et al., Huyghe et al., , Nadeau, Trepanier and Graham et al., references because the rabies virus fails is quite distinct in its structure and biological properties from adenovirus.

The rabies virus is an enveloped "budding" RNA-based rhabdovirus whereas adenovirus, as in the instant invention, is a DNA capsid based non-enveloped virus of an entirely different viral family. These viruses infect and grow differently and replicate differently. See the Declaration of Shuyuan Zhang Under 37 C.F.R. §1.132 filed March 8,

2004 in co-owned and copending U.S. Serial No. 09/203,078 a copy of which is submitted herewith as Exhibit A. In particular see paragraphs 13-15 in which Dr. Zhang who is a co-inventor in the present application addressed the relevancy of Perrin's disclosure to an adenovirus system.

Further, the fact that Perrin et al. teach the use of serum-free media, or of perfusion, roller bottles, bioreactors or microcarriers in the context of a rabies virus system does not provide any basis for employing those conditions or methods for the rabies virus system with the other aspects of the cited references to practice the claimed invention which relates to adenovirus compositions. The Perrin et al. reference or any other reference does not motivate their combination. Furthermore, a prima facie case of obviousness requires that there be a reasonable expectation of success of practicing the claimed invention based on the combination of references but expectation is lacking because of the distinctions between a rabies virus and adenovirus. For these reasons, the art-based rejections of each of pending claims 70-78, 80-104, 106-175 and 177-225 should be withdrawn.

C. The Rejections for Lack of Enablement Should Be Withdrawn.

The rejections for lack of enablement should be withdrawn because the specification provides ample direction to practice the claimed invention beyond just practice of gene therapies already known to be successful with adenoviral vectors. With respect to this rejection, the claimed invention is generally directed to "a method of treating a patient with a therapeutic adenovirus composition" which preparation has been prepared by a specifically recited process. As such, Applicants' invention is not directed to all gene therapy but relates to improved methods in treating patients with a therapeutic adenovirus composition, which methods are fully enabled as describe previously.

Applicants have previously submitted extensive evidence in the forms of the Declaration of Dr. Menander, art citations and references in their disclosure demonstrating the enablement of their claimed invention which is directed to a method of treating a patient with a therapeutic composition. Further, Applicants have explained the relevance of that evidence in their extensive accompanying remarks including those filed in the Response of October 25, 2005 which are incorporated by reference herein.

The Examiner has pointed to perceived gaps in enablement but those gaps are not in the enablement of Applicants' invention but rather in gene therapy generally. This is

improper because Applicants do not claim gene therapy generally. Rather they claim a specific method the limits of which are defined by the narrow elements of their claims. The Examiner has improperly attacked a straw-man which is "all gene therapy" rather than evaluating whether the specifically recited steps of preparing a therapeutic adenovirus composition and then administering the composition to a patient are enabled. To the extent that gene therapy is one species of one aspect of Applicants' invention that species has been fully enabled for the reasons submitted previously.

The arguments presented by the Examiner are directed to the uncertainties in gene therapy generally and not to Applicants' method. The Examiner argues that Applicants have not limited their claims but those claims are limited by their recited elements which do not encompass all gene therapies but rather only those gene therapies in which the therapeutic adenovirus preparations are prepared by the specifically recited method steps of the claims. Accordingly, the lack of enablement rejections of claims 70-78 and 80-226 should be withdrawn.

The lack of enablement rejection directed against dependent claims 71, 102, 133, 164 and 195 directed to methods achieving yields of adenovirus that are 70% ± 10% of the starting PFU of the lysate should also be withdrawn in light of the Examiner's acknowledgment that such methods are enabled by at least one preferred methodology. These dependent claims are necessarily more limited than those from which they depend and there is no obligation of Applicants to exhaust all the possible methods of achieving that preferred result when they have provided the public with a method of doing so.

D. <u>The Provisional Double Patenting Rejection Should Remain Deferred.</u>

The provisional rejection of claims 70-226 under the judicially created doctrine of obviousness-type double patenting over Zhang et al., Copending Application No. 09/203,078 (US 2004/0229335 A1) should be deferred because the pending claims in that case have not yet been patented. Accordingly, it is not necessary to take any action with respect to them at this time.

CONCLUSION

In view of the above amendments, applicants believe the pending application is in condition for allowance.

Respectfully submitted,
MARSHALL, GERSTEIN & BORUN LLP
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606
312-474-6300

By: _____
Jeffrey S. Sharp
Registration No. 31,879
Attorney for Applicants

February 27, 2006

EXHIBIT A

Declaration of Shuyuan Zhang Under 37 C.F.R. §1.132
Filed March 8, 2004 in U.S. Serial No. 09/203,078